AMENDMENTS AND UPDATES TO
HUMAN GENE TRANSFER PROTOCOLS
RECOMBINANT DNA ADVISORY COMMITTEE MEETING
MARCH 8-10, 2000

From December 1999 to early February 2000	Protocols: 9709-210 9902-284 9902-294 9903-299 9903-301 9905-315 9910-346 9910-350 9910-352	These nine protocols had a total number of 18 new sites/investigators added. Protocol 9910-346 had seven new sites/investigators. Protocols 9902-294, 9903-299, and 9903-301 had two new investigators/sites added. The remaining protocols each had one new investigator/site added.
November 11, 1999 (letter date)	9804-244 Walsh	**A Phase I Study Using Direct Combination DNA Injections for the Immunotherapy of Metastatic Melanoma.** Changes made to the clinical protocol for clarification and correction of typographical errors. Informed consent document was also revised in conjunction with the changes made to the clinical protocol.
November 12, 1999	9812-274 Camerota et. al.	**A Phase I, Multi-Center, Open Label, Safety and Tolerability Study of Increasing Single Dose of NV1FGF Administered by Intra-Muscular Injection in Patients with Severe Peripheral Artery Occlusive Disease. Sponsor: Gencell.** Amendment to allow for multiple sites of administration of a single dose. Also, protocol was amended to increase the maximal number of patients from 24 to 60.
November 17, 1999	9701-173 Croop	**A Pilot Study of Dose Intensified Procarbazine, CCNU, Vincristine (PCV) for Poor Prognosis Pediatric and Adult Brain Tumors Utilizing Fibronectin-Assisted, Retroviral-Mediated Modification of CD34+ Peripheral Blood Cells with O^6-Methylguanine DNA Methyltransferase.** Preliminary (PCR) results indicate that replication competent virus may have been present in CD34+ positive cells that were transduced and reinfused for one patient. Only the initial PCR test was positive. Two subsequent tests were negative.
November 26, 1999	9611-165 Rosenberg	**Phase I Trial In Patients With Metastatic Melanoma Of Immunization With A Recombinant Fowlpox Virus Encoding the GP100 Melanoma Antigen.** Amendment to employ a fowlpox virus encoding gp100 that contains two amino acid

		substitutions.

December 3, 1999	9902-287 Schiller and Carbone	**Phase I Pilot Trial of Adenovirus p53 in Bronchioloalveolar Cell Lung Carcinoma (BAC) Administered by Bronchoalveolar Lavage. Sponsor: NCI-Cancer Therapy Evaluation Program (NCI-CTEP)** Clarification of eligibility requirements and the informed consent was modified to reflect possible risks associated with adenoviral gene transfer.
December 21, 1999	9701-173 Croop	**A Pilot Study of Dose Intensified Procarbazine, CCNU, Vincristine (PCV) for Poor Prognosis Pediatric and Adult Brain Tumors Utilizing Fibronectin-Assisted, Retroviral-Mediated Modification of CD34+ Peripheral Blood Cells with O^6-Methylguanine DNA Methyltransferase.** Follow-up to the event reported on November 17, 1999. S+L- analysis determined that replication competent virus was not present in the transduced cells administered.
December 21, 1999	9910-350 Alberts and Gershenson	**A Phase I Dose Escalation Study of Intraperitoneal E1A-Lipid Complex (1:3) with Combination Chemotherapy in Women with Epithelial Ovarian Cancer. Sponsor: Targeted Genetics Corporation** Amendments were made to allow for additional blood collections for TNF-α level determination. Also, change in observation period from three to one week before additional patients in a cohort are treated.
December 27, 1999	9802-231 Malech	**Gene Therapy Approach for Chronic Granulomatous Disease.** Amendment to change the eligibility criteria to allow for co-enrollment on an allogeneic non-myeloablative transplantation (non gene transfer) protocol.
December 29, 1999	9806-255 Muller	**Phase I Trial of Intraperitoneal Adenoviral p53 Gene Therapy in Patients with Advanced Recurrent or Persistent Ovarian Cancer. Sponsor: National Cancer Institute - Cancer Therapy Evaluation Program (NCI-CTEP)** Amendment has been made to allow patients who have completed the dose escalation, who are experiencing palliative results with stable disease, and who did not experience significant side effects (i.e. no toxicities greater than grade 2) to receive weekly doses without a week off. Elimination of the "off week" is due to the fact that some patients experience signs of potential disease progression during the week off.
January 2000 (no cover letter)	9209-026 Walker	**A Study of the Safety and Survival of the Adoptive Transfer of Genetically Marked Syngeneic Lymphocytes in HIV Infected Identical Twins.** Dr. Jorge Tavel is now the responsible investigator; Dr. Walker has left the NIH. Update on the status of the persistence of gene modified cells. The number of months post last cell infusion ranged from 41 to 59 in the six patients. The level of gene-modified cells ranged from 0.005% of unfractionated peripheral blood lymphocytes to the limits of quantitation.
January 2000 (no cover letter)	9503-103 Morgan and Walker	**Gene Therapy for AIDS using Retroviral Mediated Gene Transfer to Deliver HIV-1 Antisense TAR and Transdominant Rev Protein Genes to Syngeneic Lymphocytes in HIV Infected Identical Twins.** Dr. Jorge Tavel is now the responsible investigator; Dr. Walker has left the NIH. Update on the status of the protocol. To date, a total of ten sets of twins have been enrolled in the study. Since the last annual update, one patient has been treated. This individual was the first to receive the new generation of vectors (amendment reported April 1999) that lack the gene encoding neomycin resistance.

		Due to the change in FDA's requirements for RCR testing and a two year history of negative results, patient serum will be banked on an annual basis. No atypical or rapid disease progression has been observed.
January 3, 2000	9810-267 Morris	**A Phase I Study of Intralesional Administration of an Adenovirus Vector Expressing the HSV-1 Thymidine Kinase Gene (AdV.RSV-TK) in Combination with Escalating Doses of Ganciclovir in Patients with Cutaneous Metastatic Malignant Melanoma.** Changes were made to the eligibility criteria to allow for more than one course of either chemotherapy or a biological response modifier.
January 4, 2000	9902-284 Ragni et al.	**Phase I Multi-Center, Single Treatment Dose Escalation Study of Factor VIII Vector [HFVIII(V)] for Treatment of Severe Hemophilia A. Sponsor: Chiron Corporation** An additional dose ($4.4x10^8$ transduction units/kg), cohort 4, has been added. This dose will be two-fold higher than that for the third dose. The increased dose is based on pre-clinical animal studies in rabbits, mice, and dogs.
January 5, 2000	9908-336 Smith	**Post-Transplant Infusion of Fibronectin-Assisted, Retroviral-Mediated Gene-Marked and Ex Vivo Expanded CD34+ Placental and Umbilical Cord Blood Cells** Change made to storage procedures for viral supernatant.
February 5, 2000	9602-146 Link et al.	**Adoptive Immunotherapy for Leukemia: Donor Lymphocytes Transduced with the Herpes Simplex Thymidine Kinase Gene for Remission Induction.** Update from Dr. Burt on patients treated. Six patients have been enrolled. Only three of the six received genetransduced cells. One of the other three patients died before cells were transduced; one patient's cells would not grow in culture; and one patient's cells are undergoing expansion now. Transgene was present at < 1.0% in two of the three patients, measured at five months and one year. In the other patient that received transduced cells, the transgene was not detected within two weeks of the infusion.
January 12, 2000	9508-116 Bozik et. al.	**Gene Therapy of Malignant Gliomas: A Phase I Study of IL-4 Gene -Modified Autologous Tumor to Elicit an Immune Response.** Inguinal lymph node biopsies have been removed as part of the study. Clarifications have been made as to the time frame for certain tests.
January 28, 2000	9804-245 Moss et al.	**A Phase I Study of Aerosolized tgAAVCF for the Treatment of Cystic Fibrosis Patients with Mild Lung Disease. Sponsor: Targeted Genetics Corporation.** An additional bronchoscopy and other tests will be performed at day 60.
February 3, 2000	9910-350 Alberts and Gershenson	**A Phase I Dose Escalation Study of Intraperitoneal E1A-Lipid Complex (1:3) with Combination Chemotherapy in Women with Epithelial Ovarian Cancer. Sponsor: Targeted Genetics Corporation** Maximal amount of DNA to be administered has been lowered (to 12mg) due to dose limiting toxicity being reached in the first patient treated under the original dosing schedule. Twenty-one day observation period before administration of DNA to either the next patient in a cohort or to the next cohort has been restored. This is a revision back to the original protocol and revises a previous amendment, dated December 21, 1999. In addition, revisions have been made to indicate that Grade 3 neutropenia was inadvertently included as grounds to delay the next round. These changes were made due to the fact that one of the chemotherapeutic agents employed in the study, paclitaxel, is a known myelosuppressant. Clarification was made that any patient

		experiencing a Grade 2-4 allergic reaction must be withdrawn from the study.